and, as a result, cytokine, which is important for developing an allergic cascade, is not produced. Studies on allergies have focused on the allergen-specific immunoreaction in the early stage, especially on the mechanisms for controlling T-cell response to allergy. An allergic response to an exogenous antigen including an allergen is initiated depending on antigen-presenting cells in the immune system. Antigen-presenting cells, including B cells, macrophages, and dendritic cells, incorporate exogenous antigens, fragment the exogenous antigens into antigen peptides (T-cell epitope peptides), and express the fragmented antigens on the cell surface together with MHC class II (HLA class II for a human) to present an antigen to antigen-specific CD4 positive helper T cells (Th cells).--

Please replace the paragraph beginning at page 3, line 22, with the following rewritten paragraph:

-- Th cells that receive the antigenic information restricted by HLA class II molecules through T-cell receptors (TCR) are activated and secrete various cytokines to proliferate by themselves and differentiate B cells into plasma cells, thereby inducing antibody production. At this time, the second signal (costimulatory signal), which is mediated by molecules other than TCR, is necessary to activate T cells. In contrast, without this signal, immunological tolerance of Th cells to an antigen is induced (June, C. et al.: Immunol Today, 15: 321, 1994).--

Please replace the paragraph beginning at page 4, line 5, with the following rewritten paragraph:

-- The decrease of T-cell response to an allergen is related to the success of hyposensitization. For example, the T-cell response in vitro to ambrosia allergen "Amb a 1" in a patient suffering from an ambrosia allergy who had undergone effective hyposensitization for ten years was dramatically decreased compared to an untreated patient. Similarly, in a patient allergic to feline epidermis antigen "Fel d 1," T- cell response specific to Fel d 1 was obviously decreased, as hyposensitization showed effects. This decrease corresponded to the decrease of sensitivity in the skin test. Furthermore, IgG and IgE antibodies specific to Fel d 1 remained at a constant level

during the treatment. These results indicated that a therapeutic agent for an allergy directly targeting antigen-specific T cells could be prepared.--

Please replace the paragraph beginning at page 7, line 20, with the following rewritten paragraph:

--Furthermore, specific T-cell epitopes binding to specific HLA class II molecules can be detected by the method of the present invention. The present inventors considered using the specific T-cell epitopes as a reagent for typing the patient's HLA class II molecules and completed the present invention. The reagent for typing the HLA class II molecules can be effectively used for selecting a peptide-based immunotherapeutic agent effective for individual patients.--

Please replace the paragraph beginning at page 8, line 7, with the following rewritten paragraph:

-- Epitopes that are "recognized" are epitopes that activate T cells. Whether T cells are activated or not can be observed by the production of cytokines, such as IL-2, IL-4 and IFN-γ or by DNA synthesis.--

Please replace the paragraph beginning at page 8, line 16, with the following rewritten paragraph:

--"Linkage disequilibrium" means the correlation found among different genes when alleles of different HLA loci are present in a single chromosome or a haplotype with higher frequency than expected by chance. Linkage disequilibrium is quantified by the difference between the expected and observed values (Δ).--

Please replace the paragraph beginning at page 9, line 2, with the following rewritten paragraph:

--In the present invention, T-cell epitopes in an allergen molecule can be mapped by, for example, culturing peripheral blood lymphocytes, T-cell lines, or T-cell clones derived from a patient sensitive to a specific allergen, together with antigen-presenting

cells and an overlapping peptide composed of about 15 to 30 amino acid residues (in which the overlapping portion is about 5 to 10 residues) which covers the whole primary structure of said allergen, determining T-cell response to these peptides by measuring the amount of [^{3}H]thymidine uptake (response by cell proliferation), and identifying the peptide to which T-cells responded. The exact epitope sites can be identified by synthesizing deletion variant peptides by deleting amino or carboxyl terminal amino acid residues of antigen peptides and monitoring the change of T-cell response to these variant peptides. Alternatively, when more than two peptides containing overlapping regions produce T-cell responses, the exact epitope sites can be identified by synthesizing new T-cell epitope peptides containing a part or all of the overlapping regions, and monitoring the change of T-cell response. The antigen peptide of the present invention preferably contains at least seven amino acid residues.--

C8 cont'd

Please replace the paragraph beginning at page 10, line 4, with the following rewritten paragraph:

C9

--An antigen peptide of the present invention induces proliferation in vitro in peripheral blood lymphocytes, T-cell lines or T-cell clones derived from an individual allergy patient having HLA class II molecules restricting said peptide. An antigen peptide of the invention does not react with an IgE antibody of a patient sensitive to the allergen from which said peptide is derived. The antigen peptide of the present invention can induce antigen-specific T-cell anergy by the administration of the antigen peptide and thereafter can induce immunological tolerance at any time when challenge with a recombinant or natural allergen derived from said antigenic peptide is made. Furthermore, once an antigen peptide of the present invention is administered to an individual sensitized by an allergen, immunological tolerance in the individual can be induced at any time thereafter by challenging with said allergen. These facts indicate that the antigenic peptide of the present invention induces an antigen-specific immunological tolerance in vitro and is useful for peptide-based immunotherapy of an allergy patient.--

Please replace the paragraph beginning at page 11, line 18, with the following rewritten paragraph:

-- At present, major allergens of cryptomeria pollen allergen, Cry j 1 and Cry j 2, have been isolated and purified. cDNAs of both allergens have been isolated, and their estimated primary structures have been disclosed (International patent application published in Japan Nos. Hei 8-502163 and Hei 8-505284). T-cell epitope sites in the Cry j 1 molecule were identified based on the molecule's primary structure. A therapeutic composition for cryptomeria pollen allergy, composed of a peptide containing the epitope site as an effective ingredient, has been disclosed (International patent application published in Japan No. Hei 8-502163). It was reported that more than 90% of patients suffering from a cryptomeria pollen allergy have IgE antibodies specific to Cry j 1 and to Cry j 2; the remaining 10% of patients have IgE antibody specific to either Cry j 1 or Cry j 2 (Hashimoto, M et al.: Clin. Exp. Allergy 44: 840-841, 1995).--

C10

Please replace the paragraph beginning at page 12, line 6, with the following rewritten paragraph:

--Based on the above report, the present inventors thought that peptide-based immunotherapy by administering either Cry j 1 T-cell epitopes or Cry j 2 T-cell epitopes would not be sufficiently effective. The present inventors provided multiple epitope peptides with the minimum length effective for peptide-based immunotherapy to a cryptomeria pollen allergy caused by antigen peptides presented by HLA-DPB1*0501. HLA-DPB1*0501 is frequently present in patients suffering from Cryptomeria pollen allergy induced by Cry j 1 and Cry J 2, and antigen peptides presented by different HLA class II molecules (DR, DQ or DP) (Japanese Patent Application No. Hei 8-80702).--

C11

Please replace the paragraph beginning at page 12, line 17, with the following rewritten paragraph:

-- This multiple epitope peptide can be expected to have enhanced effectiveness in allergy patients but is ineffective for patients who do not have HLA molecules restricting an antigen peptide composed of said epitope peptides. An antigen peptide compatible

C12

C18 Cont'd

with an individual HLA type should be administered to the individual for effective peptide-based immunotherapy.--

Please replace the paragraph beginning at page 12, line 25, with the following rewritten paragraph:

C19

--Examples of combinations of the antigen peptides with types of HLA class II restriction molecules in patients suffering from a cryptomeria pollen allergy are given below. Specific examples of HLA class II molecules and their binding partner antigen peptides include:--

Please replace the paragraph beginning at page 13, line 6, with the following rewritten paragraph:

C14

--2) DRB4*0101 binds to antigen peptides p191-205 (SEQ ID NO: 7) derived from Cry j 1 and antigen peptides p16-30 (SEQ ID NO: 12) and p186-200 (SEQ ID NO: 18) derived from Cry j 2.--

Please replace the paragraph beginning at page 13, line 9, with the following rewritten paragraph:

C15

--3) DQA1*0102-DQB1*0602 binds to antigen peptides p16-30 (SEQ ID NO: 1), p146-160 (SEQ ID NO:5), p191-205 (SEQ ID NO: 7), p251-265 (SEQ ID NO: 9), and p326-340 (SEQ ID NO: 10) derived from Cry j 1 and antigen peptides p326-340 (SEQ ID NO: 21), p341-355 (SEQ ID NO: 23), and p346-360 (SEQ ID NO: 142) derived from Cry j 2.--

Please replace the paragraph beginning at page 13, line 14, with the following rewritten paragraph:

C16

--4) DPA1*0101-DPB1*0501 binds to antigen peptides p61-75 (SEQ ID NO: 2) and 211-225 (SEQ ID NO: 8) derived from Cry j 1 and antigen peptide p76-90 (SEQ ID NO: 15) derived from Cry j 2.--

Please replace the paragraph beginning at page 14, line 9, with the following rewritten paragraph:

--It has been conventionally hypothesized that there is a bias in the use of HLA class II (at the locus level) molecules that is determined by the antigen. The above studies revealed that, in principle, all DR, DQ, and DP molecules are used as restriction molecules presenting antigen peptides derived from Cry j 1 or Cry j 2, without bias.--

C17

Please replace the paragraph beginning at page 16, line 9, with the following rewritten paragraph:

--Specifically, HLA class II molecules of an allergic patient and a healthy subject can be typed as follows. Amino acid motifs of antigen peptides binding to each molecule vary depending on the HLA class II types due to their high polymorphism. HLA class II molecules of a patient and a healthy person can thus be typed by labeling antigen peptides having different binding motifs and detecting the specific binding to HLA class II molecules. Antigen peptides can be labeled by binding a known label, such as a radioisotope, an enzyme, a fluorescent label, or a luminescent label, to an amino acid residue (for example a tyrosine residue) other than the HLA anchor amino acid residues of the antigen peptides. Alternatively, biotinylated antigen peptides are detected with streptavidin (or avidin) bound to the above label. An allergic patient can be diagnosed by culturing peripheral blood lymphocytes of the subject in the presence of various antigen peptides derived from the allergen and monitoring T-cell response by, for example, adding [^{3}H]thymidine to the culture medium and measuring the amount of [^{3}H]thymidine uptake. Moreover, if T-cell response can be found in a subject (an allergic-response-positive patient), the type of the subject's HLA class II molecules restricting the antigen peptides that induced the T-cell response can be identified as the HLA class II type endowing susceptibility to said allergen in the subject. --

C18

Please replace the paragraph beginning at page 17, line 5, with the following rewritten paragraph:

--The correlation between the patient's HLA class II type and the antigen peptides identified by this method can be used to study the role of each HLA class II type in the onset of allergy or to select antigen peptides to be used in a peptide-based immunotherapeutic agent for the allergic patient.--

Please replace the paragraph beginning at page 17, line 10, with the following rewritten paragraph:

-- A peptide-based immunotherapeutic agent for a particular allergic patient whose HLA class II molecule type has been identified can be prepared by selecting an antigen peptide compatible with the HLA type of said patient, measuring the response to the peptide to proliferate peripheral blood lymphocytes derived from the patient, and comparing the level of the response of the peptide. For example, the haplotypes of HLA class I and class II of patient PB suffering from cryptomeria pollen allergy described in Example 6 are: A2/24-B39/55-Cw7/w3-DRB1*1501/0901-DRB4*0101-DRB5*0101, DQA1*0102/0301-DQB1*0602/0303, and DPA1*0101/0101-DPB1*0501/0201. When antigen peptides to be used for peptide-based immunotherapy for said patient are selected, the antigen peptides p211-225 (SEQ ID NO: 8) presented by DPA1*0101-DPB1*0501, p106-120 (SEQ ID NO: 3) presented by DBR5*0101, p191-205 (SEQ ID NO: 7) or p251-265 (SEQ IN NO: 9) presented by DQA1*0102-DQB1*0602 should be selected in Cry j 1; in Cry j 2, p76-90 (SEQ ID NO: 15) presented by DPA1*0101-DPB1*0501, p186-200 (SEQ ID NO: 18) presented by DRB4*0101, and p66-80 (SEQ ID NO: 14) presented by DRB5*0101 should be selected. Before peptide-based immunotherapy is effected using these antigen peptides, the response to these antigen peptides to proliferate peripheral blood lymphocytes derived from the patient should be measured to select the antigen peptides exhibiting a relatively high proliferation activity, which antigen is to be used for peptide-based immunotherapy.--

Please replace the paragraph beginning at page 18, line 7, with the following rewritten paragraph:

--In order to improve solubility, therapeutic or prophylactic effects, and stability of the effects, the antigen peptide of the present invention can be modified by substituting, deleting, or adding amino acid residues other than the HLA anchors without spoiling their function. A certain amino acid can be suitably substituted with Ala, Ser, Glu, or methyl amino acids, but substituent amino acids are not limited thereto. Cys residue forms a dimer through a disulfide bond and functions as a multi-binder. Therefore, immunization with a peptide containing a Cys residue may cause recognition of sites which are not originally involved in antigenicity and thereby create new epitopes. In this case, a Cys residue can be substituted with Ala, Ser, Thr, Leu, or Glu. It may also be substituted by a D amino acid or a non-natural amino acid. A vector capable of expression of a polypeptide with a peptide composed of a histidine polymer (for example, a histidine hexamer) at its N- or C-terminus has been developed. The expression product can be purified by affinity chromatography using a nickel chelating column even in the presence of a denaturant. Such an embodiment is also included in the present invention.--

Please replace the paragraph beginning at page 19, line 6, with the following rewritten paragraph:

--Figure 1 shows the overlapping peptides of Cry j 1 containing epitopes recognized by patient's T-cells. In the figure, □ indicates $2 \leq SI < 5$ and ■ $5 \leq SI$. T-cell clones were prepared from PB and PJ.--

Please replace the paragraph beginning at page 19, line 9, with the following rewritten paragraph:

--Figure 2 shows the overlapping peptides of Cry j 2 containing epitopes recognized by patient's T-cells. In the figure, □ indicates $2 \leq SI < 5$ and ■ $5 \leq SI$. T-cell clones were prepared from PB, PC and PR.--

Please replace the paragraph beginning at page 19, line 13, with the following rewritten paragraph:

C34 --Figure 3 shows the epitope sites recognized by T-cell clones which recognize Cry j 1, the molecules restricting said clones, the production of lymphokines by said clones, and Th types of said clones. In the figure, Th2 stands for IL-4/IFN-γ>10, Th1 for IFN-γ/IL-4>10, and Th0 for a level intermediate therebetween.--

Please replace the paragraph beginning at page 19, line 18, with the following rewritten paragraph:

C35 -- Figure 4 shows the epitope sites recognized by T-cell clones which recognize Cry j 1, the restriction molecules of said clones, the production of lymphokines by said clones, and Th types of said clones. In the figure, Th2 stands for IL-4/IFN-γ>10, Th1 for IFN-γ/IL-4>10, Th0 for a level intermediate therebetween, and Thp for no lymphokine production.--

Please replace the paragraph beginning at page 19, line 24, with the following rewritten paragraph:

C36 --Figure 5 shows the immune responses of CB6F1 mice to Cry j 2 when the antigen peptide p66-80 of Cry j 2 was administered to the mice.--

Please replace the paragraph beginning at page 20, line 1, with the following rewritten paragraph:

C37 --Figure 6 shows the immune responses of CB6F1 mice to Cry j 2 when the antigen peptide p186-200 of Cry j 2 was administered to the mice.--

Please replace the paragraph beginning at page 21, line 18, with the following rewritten paragraph:

C38 --When activated T cells appeared, T-cell lines specifically recognizing Cry j 1 or Cry j 2 were established by replacing the medium with RPMI-1640 medium with 200 U/ml of IL-2 (Boehringer-Mannheim) and 15% human serum and culturing the cells for an additional 14 days.--

Please replace the paragraph beginning at page 21, line 22, with the following rewritten paragraph:

--T-cell clones specifically recognizing Cry j 1 or Cry j 2 were established as follows. When the activated T cells appeared, T cells were spread in a 10-cm culture dish and selected one-by-one using a micropipet. Separately, the same nonactivated cells transfected with EB virus were treated with mitomycin C (Kyowa Hakko Kogyo) and inoculated into each well of a 96-well microculture plate at 1 x 10^5 cells/well. The above activated T cells were transferred to the 96-well plate, one cell per well. An additional 50μg/ml of Cry j 1 or 2 to 10μg/ml of Cry j 2 was added to each well and cultured for 7 days for challenge. The challenge at an interval of 7 days was repeated two or three times to establish T-cell clones.--

Please replace the paragraph beginning at page 22, line 8, with the following rewritten paragraph:

--Peripheral blood lymphocytes derived from 18 patients suffering from cryptomeria pollen allergy were challenged by Cry j 1 or Cry j 2 to establish T-cell lines specifically recognizing Cry j 1 or Cry j 2 for each individual patient. 5 x 10^4 cells of self-derived B-cell line treated with mitomycin C, 2μM of overlapping peptides, and 2 x 10^4 cells of the T-cell line were cultured in RPMI-1640 medium supplemented with 0.2 ml of 15% serum in a 96-well microplate for two days. 0.5μCi of [^{3}H]thymidine was added, and the culture medium was cultured for an additional 18 hours. The cells were collected in a glass filter with a cell harvester, and uptake of [^{3}H]thymidine was measured with a liquid scintillation counter. T cells capable of recognizing antigenic information of Cry j 1 or Cry j 2 as well as HLA class II molecules proliferated and incorporated [^{3}H]thymidine. Cells exhibiting a Stimulation Index of 2 or higher were considered to have recognized the relevant added antigen peptides.--

Please replace the paragraph beginning at page 22, line 23, with the following rewritten paragraph:

--The number of T-cell epitope sites of Cry j 1 recognized by each patient was 9.8±3.0 on average and ranged from 4 ≤15 epitopes. Using T-cell lines recognizing Cry j 2, the number of T-cell epitope sites recognized by each patient was 8.7±3.3 on average and ranged from 2 ≤13 epitopes. Since Cry j 1 is composed of 353 amino acids (International patent application published in Japan No. Hei 8-502163) and Cry j 2 is composed of 379 amino acids (JP-A No. Hei 8-47392), the above results mean that about 2.3 to 2.8 T-cell epitope sites exist per 100 amino acid residues. Each patient has different HLA class II types and therefore recognizes different T-cell epitopes depending on the HLA class II types. An epitope map was prepared by marking T-cell epitope sites on the Cry j 1 or Cry j 2 molecule T-cell epitope sites recognized by each patient on the Cry j 1 or Cry j 2 molecule. The results are shown in Figs. 1 and 2.--

Please replace the paragraph beginning at page 24, line 6, with the following rewritten paragraph:

--35 and 14 types of T-cell clones specifically recognizing Cry j 1 were established from the peripheral blood lymphocytes derived from PB and from PJ, respectively. Similarly, 31, 10, and 17 types of T-cell clones specifically recognizing Cry j 2 were established from the peripheral blood lymphocytes derived from PB, PC, and PR respectively. All of these T-cell clones were $CD3^+$, $CD4^+$, $CD8^-$, TCR-$\alpha\beta^+$, TCR-$\gamma\delta^-$, therefore, the restriction molecules were HLA class II molecules. Self-derived 5×10^4 B-cell lines treated with mitomycin C, 2μM of the overlapping peptides, and 2×10^4 T-cell clones were cultured in RPMI-1640 medium supplemented with 0.2 ml of 15% serum on a 96-well microplate for 2 days. After 0.5μCi of [^{3}H]thymidine was added, the cells were further cultured for 18 hours. The cells were collected in a glass filter by a cell harvester and uptake of [^{3}H]thymidine was measured using a liquid scintillation counter. T-cell epitopes recognized by each T-cell clone were identified by the above manipulation. Sixty-nine percent (34/49) of T-cell clones recognizing Cry j 1 proliferated in response to stimulation by the peptide containing T-cell epitopes and the antigen peptides were identified. Similarly, antigen peptides were identified among 69% (40/58) of T cell

clones recognizing Cry j 2. T-cell clones specifically recognizing Cry j 1 recognized peptides p16-30, p61-75, p91-105, p106-120, p146-160, p151-165, p191-205, p211-225, p251-265, p326-340, and p331-346. T-cell clones specifically recognizing Cry j 2 recognized peptides p16-30, p21-35, p36-50, p66-80, p76-90, p81-95, p151-165, p181-195, p186-200, p236-250, p321-335, p326-340, p336-350, p341-355, and p346-360. The results are summarized in Figures 1 and 2 (the histograms in the center).--

Please replace the paragraph beginning at page 25, line 8, with the following rewritten paragraph:

--Example 7 Identification of HLA class II restriction molecule loci--

Please replace the paragraph beginning at page 25, line 10, with the following rewritten paragraph:

--HLA class II restriction molecules were identified at the locus level by adding monoclonal antibodies specifically reacting with HLA-class II-DR, HLA-class II-DQ, or HLA-class II-DP to the proliferation response system of T-cell clones established in Example 4 so as to inhibit T cell proliferation response.--

Please replace the paragraph beginning at page 25, line 25, with the following rewritten paragraph:

--Restriction molecules of each HLA class II type of T-cell clones whose restriction molecules were identified at the locus level can be identified by using, as antigen-presenting cells, mouse L-cells transformed with the DR gene and B-cell lines that are homozygous at the DQ or DP loci.--

Please replace the paragraph beginning at page 27, line 8, with the following rewritten paragraph:

--Figures 3 and 4 show the production of IL-2, IL-4, and IFN-γ and Th types of each clone. The number of T-cell clones recognizing Cry j 1 are 12 Th2 clones, 1 Th1 clone, and 16 Th0 clones. Thus the number of Th2 was larger than that of Th1. In

contrast, the number of T-cell clones recognizing Cry j 2 are 10 Th2 clones, 8 Th1 clones, and 8 Th0 clones. Thus the number of Th1 was almost the same as that of Th2. In comparing T cell epitopes recognized by each T cell clone, the restriction molecules, and Th types, it was found that each T-cell clone was different with respect to Th type. For several T cell clones recognizing the same epitopes and same antigen-presenting molecules, both Th2 and Th1 cells were identified. These findings indicate that differentiation of T cells to Th2, Th1, or Th0 cells after stimulation by Cry j 1 or Cry j 2 is not determined by the combination of specific T-cell epitopes or specific restriction molecules. In other words, any peptide containing T-cell epitope sites can stimulate T cells and can be selected as peptides for use as a peptide-based immunotherapeutic agent.--

C36 Cont'd

Please replace the paragraph beginning at page 27, line 26, with the following rewritten paragraph:

C37

--Eight-week-old male CB6F1 mice were immunized with 10 μg of recombinant Cry j 2 (rCry j 2) together with an adjuvant (Imject Alum, PIERCE) three times every two weeks (ip). One week after the last immunization, splenocytes were prepared from three mice and combined. 0.115 μM each of 74 overlapping peptides consisting of 15 amino acid residues was cultured separately with 5 x 10^6 splenocytes in 0.2 ml of RPMI-1640 medium (10% FCS, 2 mM L-glutamine, 50 U/ml penicillin, and 50 μg/ml streptomycin) in each well of a 96-well plate (Falcon). As the control, the responses to PBS, 50 μg/ml of Cry j 1, 0.3 μg/ml of rCry j 2 were assessed. Each reagent was inoculated in three wells and cells were cultured at 37°C in 5% CO_2 for three days. Pulse labeling was performed with 0.5μCi/well of [^{3}H]thymidine for the last 6 hours and the cells were collected in a glass filter using a cell harvester (Inoteck, Bertold Japan). After the cells were dried, uptake of [^{3}H]thymidine into the cells was measured with a liquid scintillation counter (TRI-CARB 4530, Packard Japan).--

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Please replace the paragraph beginning at page 28, line 16, with the following

rewritten paragraph:

--CB6F1 mice immunized with rCry j 2 showed a strong response to rCry j 2 antigen, but did not respond to another cryptomeria pollen major allergen Cry j 1, indicating that this system was antigen-specific reaction. Of the 74 overlapping peptides tested, splenocytes from CB6F1 mice immunized with rCry j 2 showed remarkable responses to p66-80 (SEQ ID NO: 14) and p236-250 (SEQ ID NO: 19). These results indicated that p66-80 and p236-250 peptides are presented as major epitopes of Cry j 2 in CB6F1 mice. In humans, p66-80 (SEQ ID NO: 14) and p236-250 (SEQ ID NO: 19) are also major T cell epitope peptides. Thus, CB6F1 mice can be a useful model animal to evaluate the effectiveness of peptide compositions to be used in peptide-based immunotheraphy for cryptomeria pollen allergy.--

C38

Please replace the paragraph beginning at page 29, line 4, with the following rewritten paragraph:

--Three mg of p66-80 peptide (SEQ ID NO: 14) dissolved in physiological saline was subcutaneously administered to an eight-week-old male mouse twice at an interval of 5 days. Similarly, the same volume (100 µl) of physiological saline was administered to mice of the control group. Both the peptide-administered group and a control group had eight mice. Five days after the second peptide administration, 50 µg of rCry j 2 mixed with an adjuvant, Imject Alum, was subcutaneously administered to all mice for immunization. One week after the immunization, splenocytes were prepared from each mouse. 5 x 10^6 splenocytes were cultured together with 3 µg/ml of rCry j 2 in 0.2 ml of RPMI medium (10% FCS, 2mM L-glutamine, 50 U/ml penicillin, and 50 µg/ml streptomycin) in each well of a 96-well plate (Falcon). As the control, the cells were cultured in the same medium containing no rCry j 2. Uptake of [^{3}H]thymidine was measured as described in Example 10.--

C39

Please replace the paragraph beginning at page 29, line 19, with the following rewritten paragraph:

--When p66-80 (SEQ ID NO: 14) was subcutaneously administered to CB6F1 mice before antigen stimulation by rCry j 2, immune response of the T cells was significantly inhibited compared to the physiological saline-administered group ($p<0.01$) (Figure 5). This result indicated that in the mouse model p66-80 (SEQ ID NO: 14) system showed a preventive effect in peptide-based immunotherapy for treating cryptomeria pollen allergy.--

Please replace the paragraph beginning at page 29, line 26, with the following rewritten paragraph:

--Example 12 In vivo immune response to antigen peptide p236-250 (peptide no. 48) (SEQ ID NO: 19)--

Please replace the paragraph beginning at page 30, line 2, with the following rewritten paragraph:

--Three mg of p236-250 peptide (SEQ ID NO: 19) dissolved in physiological saline was subcutaneously administered to a six-week-old male mouse twice at an interval of 5 days. As a control, the same volume (200 µl) of physiological saline was administered to mice in the same manner as above. Both the peptide-administered group and the control group had eight mice. Five days after the second peptide administration, 50 µg of rCry j 2 mixed with adjuvant Imject Alum was subcutaneously administered to all mice. One week after the immunization, splenocytes were prepared from each mouse. 5×10^6 splenocytes were cultured together with 3 µg/ml of rCry j2 in 0.2 ml of RPMI medium (10% FCS, 2mM L-glutamine, 50 U/ml penicillin, and 50 µg/ml streptomycin) in each well of a 96-well plate (Falcon). As a control, the cells were cultured in the same medium containing no rCry j 2. Uptake of [^{3}H]thymidine was measured as described in Example 10.--

Please replace the paragraph beginning at page 30, line 17, with the following rewritten paragraph:

--When p236-250 (SEQ ID NO: 19) was subcutaneously administered to CB6F1 mice before antigenic stimulation by rCry j 2, immune response of the T cells was significantly inhibited compared to the physiological saline- administered group ($p < 0.05$) (Figure 6). This result indicated that in the mouse model system p236-250 (SEQ ID NO: 19) showed a preventive effect in peptide-based immunotherapy for treating cryptomeria pollen allergy.--

Please replace the paragraph beginning at page 31, line 2, with the following rewritten paragraph:

--According to the present invention, an antigen peptide that binds to a haplotype of HLA class II molecules of an allergic patient can be used as a peptide-based immunotherapeutic agent for that patient. The present invention enables the optimal peptide-based immunotherapy for individual patients. Thus the effectiveness of peptide-based immunotherapy is expected to be remarkably improved. Furthermore, the present invention provides a peptide-based immunotherapeutic agent effective for a patient who cannot be treated by peptide-based immunotherapy using major antigen peptides recognized in a specific patient population.--

In the claims:

Claims 16 and 17 are amended.

In the drawings

Please substitute Figs. 1 and 2 presently in the application with the enclosed copies of Figs. 1 and 2 containing amendments shown in red.